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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,256	GRAHAM ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *4-9 and 11-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20041207;20050128*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice of Non-Compliant Amendment.

DETAILED ACTION

1. The election with traverse filed May 1, 2008, is acknowledged and has been entered.

Applicant has elected the invention of Group IV, claim 10, drawn to drawn to a method for inhibiting or reducing the proliferation of prostate cancer cells, or to a method for treating prostate cancer, said method comprising administering to the cells or to a subject in need of treatment a cPLA2-IIA inhibitor, wherein said cPLA2-IIA inhibitor is c(2NapA)LS(2NapA)R.

Claims 1-3 are linking claims, linking the inventions of Groups I-V, whereas claims 5-9 are linking clams that link the inventions of Groups II, III, and IV.

2. The amendment filed May 1, 2008, is acknowledged and has been entered in part. Claim 10 has been amended.

3. Claims 1-17 are pending in the application. Claims 4 and 11 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 1, 2008.

4. Claims 1-3, and 5-10 are currently under prosecution.

Information Disclosure Statement

5. The information disclosures filed December 7, 2004, and January 28, 2005, have been considered. An initialed copy of each is enclosed.

Election/Restrictions

6. Upon reconsideration of the restriction and election requirement set forth in the Office action mailed April 1, 2008, the inventions of Groups II, III, and IV have been rejoined; and thus to that extent the requirement has been withdrawn.

7. Applicant's arguments traversing the propriety of the restriction and election requirement set forth in the Office action mailed April 1, 2008, are acknowledged.

Applicant's arguments have been carefully considered but are either moot or have not been found persuasive:

Applicant has argued that the claims are directed to a method for inhibiting or reducing the proliferation of prostate cancer, or for treating prostate cancer, wherein said method comprises administering to the cells or subject in need thereof an inhibitor of the secreted form of PLA_2, not the cytosolic form of PLA_2. However, contrary to Applicant's argument claim 1 is drawn to 1 a method of inhibiting or reducing the proliferation of prostate cancer cells, said method comprising administering to the cells a PLA_2 inhibitor, and not necessarily an inhibitor of a secreted isoform of PLA_2. Similarly, claim 2 is drawn to a method for the treatment of prostate cancer, said method comprising administering to a subject in need thereof a PLA_2 inhibitor, and again not necessarily an inhibitor of a secreted isoform of PLA_2.

As explained in the Office action mailed April 1, 2008, the inventions of Groups I-IX appear to be linked by a common concept, or special technical feature, namely contacting prostate cancer cells with a PLA_2inhibitor, so as to inhibit the proliferation of the cells, as recited in claim 1. However, Herrmann et al. (*Exp. Ceil Res.* 1997; 234: 442-451) teaches contacting prostate cancer cells with a PLA_2 inhibitor (i.e., AACOCF3), so as to inhibit the proliferation of the cells; see entire document (e.g., page 445, Figure 3). Accordingly, the technical feature that appears to link the inventive concepts of the inventions of Groups I-IX does not constitute a special technical feature as defined by PCT Rule 13.1, as it does not define a contribution over the prior art.

As such, the special technical features of the inventions of Group I, II, III, IV, and V, for example, are deemed inhibiting or reducing the proliferation of prostate cancer cells, or treating prostate cancer by a process method comprising administering to the cells or to a subject in need of treatment a cPLA2-α2 inhibitor, or cPLA2-IIA inhibitor, wherein said cPLA2-IIA inhibitor is selected from cFLSYK, cFLSYR, and c(2NapA)LS(2NapA)R, respectively, where, as mentioned above, claims 1-3 are linking

claims, linking the inventions of Groups I-V, and claims 5-9 are linking clams that link only the inventions of Groups II, III, and IV.

Accordingly, the restriction and election requirement set forth in the Office action mailed April 1, 2008, is still deemed proper and therefore made FINAL.

Priority

8. Applicant's claim under 35 U.S.C. §§ 119(e) and/or 120, 121, or 365(c) for benefit of the earlier filing date of the benefit of PCT Application No. PCT/AU03/00719, filed June 10, 2003, which claims benefit of Australia Patent Application No. PS 2826, filed June 7, 2002, is acknowledged.

However, claims 1-3 and 5-10 do not properly benefit under §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). See M.P.E.P. § 201.11.

In addition, it is aptly noted that claim 3 does not properly benefit from the earlier filing date of Australia Patent Application No. PS 2826 because that document does not describe the claimed invention. Moreover it does not disclose that the prostate cancer cells are androgen independent, nor does it describe experiments that utilized androgen independent prostate cancer cell lines, such as PC3.

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely January 14, 2005.

Specification

9. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See M.P.E.P. § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is MetaPhor™; see, e.g., paragraph [0135] of the published application[1].

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

10. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

An example of such an impermissible disclosure appearing in this application is found in the specification at paragraph [0140] of the published application.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See M.P.E.P. § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 C.F.R. § 1.57.

[1] U.S. Patent Application Publication No. 2008/0113343 A1.

11. The specification is objected to because of the following formality:

At paragraph [0131] of the published application, the specification erroneously cites: "Church, W. B. et al. (2001), J. Biol. Chem. 276:33156-33614". The pages numbers are listed incorrectly.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims 1-3 fail to correspond in scope with that which Applicant regards as the invention can be found in the reply filed May 1, 2008. In that paper, at page 7, Applicant has stated:

> In fact, these claims are directed to inhibitors of the **secreted** form of PLA_2 not the cytosolic form, so they are sPLA2-IIA inhibitors [emboldened and underscored in the original]. This is a critical point because the citation raised in justifying the Restriction Requirement (Hermann et al., 1997, a copy of which is enclosed) discloses so-called "selective" inhibitors of **c**PLA_2 [emboldened and underscored in the original].

This statement indicates that the invention is different from what is defined in the claims 1-3 because claims 1 and 2 are directed to "a PLA_2 inhibitor", and notably claim 5 is drawn to the method of claim 1, wherein the PLA_2 inhibitor is "a $sPLA_2$-IIA inhibitor".

In addition, Applicant has further remarked that the PLA_2 inhibitor described by Hermann et al. is not specific since it inhibits other enzymes. This statement, too, indicates that the invention is different from what is defined in claims 1-3 because none of those claims recite a limitation that the inhibitor exclusively inhibits PLA_2.

Accordingly, Applicant's remarks provide evidence that claims 1-3 fail to correspond in scope with that which Applicant regards as the invention.

14. Claims 1-3 and 5-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 and 5-10 are indefinite for the following reasons:

(a) Claims 1-3 are indefinite because as discussed in the above rejection, Applicant's remarks at page 7 of the response filed May 1, 2008, provide evidence that claims 1-3 fail to correspond in scope with that which Applicant regards as the invention.

If claims 1-3 are directed to an inhibitor of a soluble isoform of PLA_2, but not a cytoplasmic isoform, as Applicant's remarks suggest, it is apparent that the term "PLA_2" cannot be used to identify with the requisite clarity and particularity the enzyme to which the claims are directed.

Notably, too, the use of laboratory designations only to identify a particular polypeptide or a class of polypeptides renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct polypeptides.

In addition, it is aptly noted that the same term is often used in the art to describe not one polypeptide, but rather a plurality of polypeptides, which might be structurally and/or functionally related, but otherwise distinct. For example, the same terms are often used to describe various isoforms that are encoded by a single gene, which result from translation of alternatively spliced transcripts of that gene; as another example, the same terms are frequently used to identify polypeptides that occur in different species of animals, which although sharing certain structural and/or functional characteristics have distinct structures and/or functions (e.g., orthologs and paralogs).

That is evidently the case here since "PLA_2" is a term used to identify the particular isoform to which the claims 5-10 are specifically directed, namely an isoform designated "$sPLA_2$-IIA". In addition, it is evident that the term "PLA_2" is used to describe variants that are localized to the cytoplasm (e.g., the "$cPLA_2$" isoforms, as referred to in Applicant's remarks at page 7 of the reply filed May 1, 2008), as well as to a plurality of secreted isoforms, as recited in claim 6 (i.e., "$sPLA_2$-IIA" and the "other $sPLA_2$ proteins").

Not inconsistently the specification discloses, "PLA2 constitutes a large and diverse family of enzymes that catalyse the hydrolysis of membrane phospholipids at the sn-2 position to release fatty acids and lysophospholipids" (page 3, lines 1-3)[2].

35 U.S.C. § 112, second paragraph, requires the claim define the metes and bounds of the subject matter that is regarded as the invention with such clarity and particularity to permit the skilled artisan to know or determine infringing subject matter; because the terms used to describe the polypeptides to which the claims are directed do not unambiguously identify those polypeptides, this requirement has not been met.

In accordance with a recent decision by the Federal Circuit (*Halliburton Energy Services Inc. v. M-I LLC*, 85 USPQ2d 1654, 1658 (Fed. Cir. 2008)):

> 35 U.S.C. § 112, ¶ 2 requires that the specification of a patent "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." Because claims delineate the patentee's right to exclude, the patent statute requires that the scope of the claims be sufficiently definite to inform the public of the bounds of the protected invention, i.e., what subject matter is covered by the exclusive rights of the patent. Otherwise, competitors cannot avoid infringement, defeating the public notice function of patent claims. Athletic Alternatives, Inc. v. Prince Mfg., Inc., 73 F.3d 1573, 1581 (Fed. Cir. 1996) ("[T]he primary purpose of the requirement is 'to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their [respective] rights.'") (quoting Gen. Elec. Co. v. Wabash Appliance Corp., 304 U.S. 364, 369, (1938)). The Supreme Court has stated that "[t]he statutory requirement of particularity and distinctness in claims is met only when [the claims] clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." United Carbon Co. v. Binney & Smith Co., 317 U.S. 228, 236 (1942).

To which members of the large family of "PLA_2" enzymes having substantially different expression patterns, structures and functions are the claims directed? Which members of the family are the targets of the inhibitor to which the claims are directed? Which members of the family must be inhibited, so as to achieve the claimed objective of practicing the invention, namely the inhibition or reduction of proliferation of prostate cancer cells and/or therapeutic effect in subjects in need of treatment?

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[2] Markova et al. (*Oncogene*. 2005 Sep 22; **24** (42): 6450-6458) discloses PLA_2 enzymes are subdivided into several groups that include, but are not limited to, secreted PLA_2 (Groups IB, IIA, IIC, IID, IIE, IIF, III, V, X and XII—typically low molecular weight, <30 kDa proteins) and cytosolic PLA_2 (Group IVα–IVδ high molecular weight, >80 kDa proteins); see entire document (e.g., page 6450, column 2).

It is suggested that this issue *might* be remedied by amending the claims to include a recitation of the amino acid sequence of the polypeptides (enzymes) by reference to one or more specific sequence identification numbers of amino acid sequences of the polypeptides, as set forth in the Sequence Listing, because the amino acid sequence of a polypeptide is a unique identifier that unambiguously defines a given polypeptide.

However, because many members of the "PLA_2" have more than one functional activity, it may not be apparent which activity of the polypeptide is necessarily inhibited by the "PLA_2 inhibitor" to which the claims are directed, so as to achieve the claimed objective; and in that case, it might not be sufficient to simply identify the molecular target of the inhibitor, but also necessary to identify the particular activity of the targeted "PLA_2" family member, which must be inhibited, such that the proliferation of prostate cancer cells is inhibited or reduced and/or there is a therapeutic effect in the subject.

(b) Claim 2 is indefinite because the claim recites the phrase "in need thereof".

The phrase "in need thereof" is not defined by the claim; so it is unclear of what the subject is required to be in need. Moreover, the specification does not provide a standard for ascertaining whether or when a subject is in need, and is also void of guidance indicating how one can determine or know when a subject is in need.

If the subject must be in need of therapy, must the subject have prostate cancer? Must the subject have prostate cancer that is refractory to conventional, first-line therapy? When is the subject in need of therapy?

Given the ambiguity with which the claim may be construed, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention; and moreover it is submitted that the claim fails to delineate the metes and bound of the subject matter that is regarded as the invention with the requisite clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, so as to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

It is suggested that it would be remedial to amend claim 2 to recite, for example, the phrase "administering to a subject diagnosed with prostate cancer and requiring

treatment for said cancer" or the phrase "administering to a subject determined to have prostate cancer that requires therapeutic intervention".

(c) Claims 5-10 are indefinite because the claims use of the designation "$sPLA_2$-IIA" as the sole means of identifying the polypeptide (enzyme) to which the claims refer. Again, the use of laboratory designations only to identify a particular polypeptide or a class of polypeptides renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct polypeptides.

In addition, as already explained, the same term is often used in the art to describe not one polypeptide, but rather a plurality of polypeptides, which might be structurally and/or functionally related, but otherwise distinct.

Support of this position is found in Markova et al. (*Oncogene*. 2005 Sep 22; 24 (42): 6450-6458). Markova et al. discloses that "$sPLA_2$-IIA" has been identified as a "tumor modifier", which confers resistance to tumorigenesis by modifying the expressivity or effects of the expression of an oncogene; see entire document (e.g., the abstract; and page 6451, column 1). Markova et al. describes variants of "$sPLA_2$-IIA", which have disparate activities, as having markedly different roles in tumorigenesis; see, e.g., the abstract. For example, Markova et al. describes neoplasia-resistant strains, which were then shown by sequencing to carry variant wild-type alleles of the *Pla2g2a* gene encoding "$sPLA_2$-IIA"; and in contrast, strains associated with greater numbers of polyps were found to carry mutant alleles (abstract). Accordingly, Markova et al. teaches that the disparate activity levels observed in different strains correlate with differences in the amino acid sequence of the sPLA2-IIA protein, as well as with the different tendencies of resistant and susceptible strains to develop polyps; see, e.g., page 6456, column 2.

In light of such evidence, it is apparent that the claims do not clearly and particularly identify the "$sPLA_2$-IIA" polypeptide(s) that are necessarily targeted by the inhibitor, so that inhibition of the activity of the polypeptide(s) results in the inhibition or reduction in the proliferation of prostate cancer cells and/or therapeutic effect.

Therefore, because 35 U.S.C. § 112, second paragraph, requires the claim define the metes and bounds of the subject matter that is regarded as the invention with such clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, and because the term used to describe the polypeptides to which the claims are directed do not unambiguously identify those polypeptides, this requirement has not been met.

This issue could be remedied by amending the claims to include a recitation of the amino acid sequence of the polypeptides by reference to one or more specific sequence identification numbers of amino acid sequences set forth in the Sequence Listing because the amino acid sequence of a polypeptide is a unique identifier that unambiguously defines a given polypeptide; but Applicant is cautioned against introducing new matter into the specification by the addition of amendatory material, which is not properly supported by the specification, as originally filed.

However, because the "sPLA$_2$-IIA" polypeptide(s) to which the claims are directed have more than one function, it may not be sufficient to merely identify the polypeptide(s), but might instead be imperative that the activity that must be inhibited by the inhibitor is identified.

Which one the plurality of activities of "sPLA$_2$-IIA" must be inhibited in order to inhibit or reduce the proliferation of prostate cancer cells? Which activities must be inhibited by the inhibitor, such that the inhibitor is used to treat prostate cancer in a subject?

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1-3 and 5-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or

> a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In this instance, the claims are drawn to a method of inhibiting or reducing the proliferation of prostate cancer cells and/or treating prostate cancer in a subject. According to claims 1-3 the process comprises administering to the cells and/or the subject "a PLA_2 inhibitor"; according to claims 5-10, the inhibitor inhibits a "$sPLA_2$-IIA" polypeptide; according to claims 6-8 the inhibitor is a conformationally constrained molecule, such as a cyclic peptide or derivative thereof, which comprises amino acids residues 70-74 of a human the "$sPLA_2$-IIA" polypeptide or their equivalents in other the "$sPLA_2$" polypeptides; and according to claims 9 and 10, the inhibitor is selected from a finite number of cyclic peptides having a particular formula, including cyclic peptides comprising the amino acid sequences of F-L-S-Y-K, F-L-S-Y-R, and 2NapA-L-S-2NapA-R^3.

As explained in the above rejection of claims, as failing to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, it cannot be ascertained which particular polypeptides are identified by the terms "PLA_2" and "$sPLA_2$-IIA", but it is presumed that the claims are directed to any of a plurality of various structural and/or functional variants that are expressed in any of a number of different types of cells and/or tissues in any of a number of different animals.

As further explained above, the term "PLA_2" is actually used in the art to designate a rather large family of polypeptides having substantially different structures and/or functions, including the products of genes that are orthologs and/or paralogs

expressed in different species of animal, as well as allelic variants, mutants, and/or alternatively spliced and/or processed isoforms expressed in the same or different cells and/or tissues of the same animal.

A search in the ENTREZ GENE database of the National Center for Biotechnology Information (NCBI) of the National Library of Medicine (NLM) using the term "PLA2" as a query revealed 178 different listings describing genes encoding phospholipase A2 or a homolog thereof in different organisms, though not necessarily animals.

Notably, too, the specification discloses that the methods of the present invention encompass targeting “any PLA_2 enzyme" (paragraph [0047] of the published application).

However, inasmuch as the cells are prostate cells, it might stand to reason that the cells are mammalian, though not necessarily human; and in the case of claim 2, since the invention is intended to treat prostate cancer, it might be presumed the subject is a mammal, if not a human.

Nonetheless, according to Murkami et al. (*J. Biochem.* 2002 Mar; **131** (3): 285-292), the “PLA_2” family includes at least 19 different enzymes, which catalyze the hydrolysis of the sn-2 position of membrane glycerophopholipids to yield arachidonic acid; see entire document (e.g., the abstract). The secreted subfamily of PLA_2 enzymes includes 10 isozymes, which are low molecular weight, calcium cation dependent enzymes that have been implicated in a number of different processes such as modification of eicosanoid generation, inflammation, host defense, and atherosclerosis; see entire document (e.g., the abstract). There is the subfamily of cytosolic PLA_2 enzymes consists of three enzymes, the calcium independent subfamily of PLA_2 enzymes includes two more enzymes, and finally Murkami et al. teaches a subfamily of four members representing a relatively unique group of platelet-activating factor acetylhydrolases (abstract). Despite catalyzing the hydrolysis of the *sn*-2 position of

[3] “2NapA” denotes a non-naturally occurring analogue of alanine, namely 2-naphthylalanine; see paragraph [0026] of the published application.

membrane glycerophopholipids, Murkami et al. describes the family, as a whole, as having rather different structures and biological functions; see, e.g., page 286, Figure 1.

Then, Masuda et al. (*Biochim. Biophys. Acta.* 2005; 1736: 200-210) discloses that members of the family of PLA_2 enzymes are diversely expressed by cells, even with in the same tissue types and/or organs; see entire document (e.g., the abstract). For example, Masuda et al. teaches in gastric glands exhibiting metaplasia, "$sPLA_2$-IIA" was localized in the glandular base, "$sPLA_2$-IID" and "$sPLA_2$-IIV" were in the glandular body epithelium, "$sPLA_2$-IIE" and "$sPLA_2$-IIF" were in goblet cells in the foveolar epithelium, and "$sPLA_2$-IIX" was in both glandular body epithelial cells and foveolar epithelial goblet cells; see, e.g., the abstract. Masuda et al. teaches that such variations in the cell type-specific expression patterns of different members of the family of PLA_2 enzymes, even within the same tissues, suggest that each has a unique biological role.

Accordingly, claims 1-3 are still rather broadly directed to inhibitors of any of a very large number of structurally and/or functionally disparate polypeptides, and not all of which are expressed in all prostate cells in male animals[4].

For example, Suzuki et al. (*J. Biol. Chem*. 2000 Feb 25; **275** (8): 5785-5793) describes their discovery of a new gene encoding an isoform of the secreted "PLA2" subfamily that has been designated "$sPLA_2$-IID", which is only expressed in brain, heart, lung, and placenta, whereas the gene encoding "$sPLA_2$-IIA" is more broadly expressed; see entire document (e.g., the abstract). Somewhat similarly, Murkami et al. (*supra*) describes "sPLA2-IIF" as an isozyme having a unique structure, which is expressed only in the testis of mice, but expressed at low levels in a plurality of tissues in humans; see, e.g., page 287, column 2. Then, although claims 5-10 are more narrowly directed to a "$sPLA_2$-IIA inhibitor", it appears that not even "$sPLA_2$-IIA" is always expressed by prostate cancer cells. Menschikowski et al. (*Neoplasia*. 2008 Mar; **10** (3): 279-286) describes their recent discovery that while LNCaP and PC-3 prostate cancer cells

[4] Notably the claims do not require the prostate cells to express the polypeptide that is targeted by the claimed "PLA2 inhibitor"; and in the case of claim 2, the subject need not be human, or even male and/or have a prostate.

constitutively express the gene encoding "$sPLA_2$-IIA", it is not expressed in DU-145 prostate cancer cells; see entire document (e.g., the abstract).

Notably, the absence of expression of the gene encoding "$sPLA_2$-IIA" in DU-145 prostate cancer cells is apparently due to epigenetic mechanisms. Menschikowski et al. (*supra*) teaches that re-expression of the gene in DU-145 cells was observed following treatment of the cells with 5-aza-2'-deoxycytidine, which suggests that the gene is silenced in those cells by DNA methylation; see, e.g., the abstract.

Logically, if the prostate cancer cell does not express the "PLA_2" or "$sPLA_2$-IIA", the inhibitor cannot reasonably be expected to inhibit the proliferation of prostate cancer cells, either *in vitro* or *in vivo*, or the specification would not reasonably convey to the skilled artisan that Applicant had possession of such an embodiment of the claimed invention at the time the application was filed since it only describes the inhibition of LNCaP and PC-3 cells that express "$sPLA_2$-IIA" by contacting those cells *in vitro* with two particularly described inhibitors of "$sPLA_2$-IIA", namely "cFLSYR" and "c(2Nap)LS(2Nap)R"; see, e.g., paragraph [0147]-[0149] of the published application.

Not inconsistently the specification teaches the proliferation of DU-145 prostate cancer cells was not affected by any of the inhibitors (paragraph [0148]; and Figure 4); yet, as indicated, the claims are not limited to prostate cancer cells that express the "PLA2" that is targeted by the inhibitor, or to prostate cancer cells that are sensitive to the inhibitory effects of the inhibitor.

As also addressed in the above rejection of claims, as failing to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, it cannot be ascertained which particular function or activity of the "PLA_2" or "$sPLA_2$-IIA" is necessarily inhibited by the inhibitor, such that the proliferation of prostate cancer cells is inhibited or reduced and/or the inhibitor is effective to treat prostate cancer in a subject.

If, as discussed in the paragraphs above, each member of the family of "PLA_2" enzymes has a unique niche in cellular physiology and different biological functions, if not specific activities, then it follows that the inhibitors to which the claims are directed

must have widely varying functions as well, especially if the inhibitors are effective to inhibit the proliferation of prostate cancer cells.

Human sPLA2-IIA, for example, has the catalytic activity that characterizes all members of the family of phospholipase A_2 ("PLA_2") enzymes, namely the ability to hydrolyze the *sn*-2 position of membrane glycerophopholipids to yield arachidonic acid and free fatty acids, but this enzyme also has other activities, including, for example, the ability to bind to heparin and cell surface associated heparan sulfate proteoglycans (e.g., membrane anchored glypicans), which stimulates an autocrine feedback loop that apparently induces transcription of the gene encoding $sPLA_2$-IIA, an effect that is independent of the hydrolytic activity of the enzyme[5].

Another activity of $sPLA_2$-IIA, which is apparently independent of its catalytic activity, is its ability to bind to M-type PLA_2 receptor, which transduces signals that lead to such disparate effects in various cell types that include increased expression of COX-2, release of cytokines, and activation of EGFR. $sPLA_2$-IIA also functions to activate $cPLA_2$; and in at least colon cancer models, it appears to act as a modifier of the oncogenic effects of APC mutations, actually suppressing polyp formation and ultimately tumorigenesis.

Notably, Finjeman et al. (*Front. Biosci.* 2008 May 1; **13**: 4144-4174) has very recently reviewed the complexity of $sPLA_2$-IIA, as its roles have been studies in a number of tissues of different mammals, including mouse and human.

Despite the fact that $sPLA_2$-IIA and other $sPLA_2$ enzymes have so many different biological roles, and despite the fact that the claims are broadly directed to an inhibitor of any of these various different enzymes, the specification describe the actual biological functions and/or specific activities of each of the different members of the family of "PLA2" enzymes that must be inhibited by the inhibitors, so as to inhibit the proliferation of prostate cancer cells; and as such, the specification does not describe with the clarity and particularity necessary to satisfy the written description requirement the genus of inhibitors, as a whole, to which the claims are directed.

For example, the specification has not described an inhibitor that inhibits an activity or function of a "PLA2" enzyme encoded by a gene that is expressed in the androgen independent prostate cancer cell line, DU-145.

In this regard, it is noteworthy that Rose et al. (*Prostate*. 1991; **18** (3): 243-254) teaches PC-3 cell growth was inhibited by omega-3 dietary fatty acids present in fish oils, namely docosahexaenoic acid and eicosapentaenoic acid in a dose-dependent manner, but the growth of DU-145 cells, which is also androgen independent, was less sensitive to such treatment; see entire document (e.g., the abstract). In addition to this difference, Rose et al. reports that PC-3 cells are stimulated by linoleic acid, whereas Du-145 cells are not; see, e.g., page 245.

The differences described by Rose et al. (*supra*) between different androgen independent prostate cancer cell lines, together with the disclosure by Menshikowski et al. (*supra*) and the findings reported in the specification, underscore the high level of unpredictability in the art, and add to a bevy of data suggesting that the results of *in vitro* studies must be interpreted cautiously, since those results are not always extrapolated to predict the response of prostate cancer cells *in vivo*[6].

Menschikowski et al. (*supra*) points out an additional difference that was observed between LNCaP cell and PC-3 cells, which should be considered as well. In particular, Menschikowski et al. (*supra*) teaches that the expression of the gene encoding "sPLA$_2$-IIA" in PC-3 cells is upregulated upon exposure of the cells to γ-interferon (IFN-γ), yet the gene in LNCaP cells is not; see, e.g., the abstract.

Given the fact that prostate cancer cell lines LNCaP, PC-3, and DU-145 have such different phenotypes, it is submitted that none can be fairly considered representative of the genus of prostate cancer cells to which the claims are directed, and particularly not those that occur in subject afflicted by the disease. If so, the

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[5] See Jaulmes et al. (*Arterioscler. Thromb. Vasc. Biol.* 2005 Jun; 25 (6): 1161-1167); entire document (e.g., the abstract; and page 1161, column 2).

[6] Support for this position is found in the disclosure by Kelland et al. (*Eur. J. Cancer.* 2004 Apr; **40** (6): 827-836) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). Kelland et al. discusses, despite the limitations of xenograft models, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even in silico methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2).

disclosure in this application that the cyclic peptides "cFLSYR" and "c(2Nap)LS(2Nap)R") are capable of inhibiting the proliferation of LNCaP and PC-3, but not DU-145 should not be considered reasonably descriptive of the claimed subject matter, as a whole.

Furthermore, although the particularly described inhibitors (i.e., "cFLSYR", "cFLSYK", and "c(2Nap)LS(2Nap)R") have structures similar to an inhibitor of "$sPLA_2$-IIA" described by the prior art[7], namely the linear peptide having the amino acid sequence of residues 70-74 of a purified human $sPLA_2$-IIA enzyme, which consists of SEQ ID NO: 5 (F-L-S-K-Y), the claimed inhibitors need not have any particular structure, and might be composed of any material. The inhibitors are not necessarily peptides in other words, and might instead be small molecules or antibodies, for example.

Given the fact that the inhibitors may have any structure, and may act to inhibit the biological functions and/or specific activities of such a disparate plurality of enzymes, it is apparent that none of the particularly described inhibitors is fairly considered representative of the genus of inhibitors, as a whole. In fact, because the specification does not disclose any particularly identifying structural features that correlate with the ability of such materially and structurally different molecules to inhibit the function or activity of the "PLA_2" or "$sPLA_2$-IIA" enzyme to which the claims are directed, the skilled artisan could not immediately envision, recognize or distinguish at least a substantial number of the members of the claimed genus of inhibitors.

Accordingly, Applicant is reminded that "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes with the clarity and particularity the genus of "PLA2" or "$sPLA_2$-IIA" inhibitors that can be used to inhibit or reduce the proliferation of prostate cancer cells and/or achieve the claimed therapeutic effect in subjects afflicted with

[7] See, e.g., Tseng et al. (*J. Biol. Chem.* 1996 Sep 27; **271** (39): 23992-23998); see entire document (e.g., the abstract). Tseng et al. discloses that the "70-74-peptide" (F-L-S-Y-K) forms a non-covalent complex

prostate cancer. *A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.*

While the written description requirement can by satisfied without an actual reduction to practice, the disclosure of a catalog of potentially effective substances that might be found to be useful in practicing the claimed invention does not fulfill the written description requirement. Recognizing that the claims are drawn to a method comprising administering to prostate cancer cells and/or a subject an unspecified substance having the ability to inhibit an activity of "PLA2" or "$sPLA_2$-IIA", so as to be therapeutically effective, it is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to inhibit an activity of "PLA2" or "$sPLA_2$-IIA" to achieve a reduction in the proliferation of prostate cancer cells in a subject, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d

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with the amino-terminus of low molecular weight, type II $sPLA_2$ enzymes to inhibit phospholipid hydrolysis

1886 1894 (CAFC 2004). The claimed method depends upon finding a compound that has the ability to inhibit an activity of "PLA2" or "$sPLA_2$-IIA", which can be used to inhibit or reduce the proliferation of prostate cancer cells and/or to achieve therapeutic effect in treating prostate cancer using the claimed process; without such a compound, it is impossible to practice the invention.

In addition, although the skilled artisan could potentially identify agents that might be used in practicing the claimed invention by screening for substances that are capable of inhibiting an activity of "PLA2" or "$sPLA_2$-IIA" and, in turn, the proliferation of prostate cancer cells, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Absent the adequate description of a representative number of members of the genus of "PLA2" or "$sPLA_2$-IIA" inhibitors to which the claims are directed, the supporting disclosure amounts to no more than a mere invitation to identify a substance that can be used as an agent for treating cancer by inhibition of an activity of "PLA2" or "$sPLA_2$-IIA".

Guidelines states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show

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in a dose-dependent manner (abstract).

that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of substances having the ability to inhibit an activity of "PLA2" or "$sPLA_2$-IIA" and, in turn, the proliferation of prostate cancer cells, so as to be capable of causing a beneficial therapeutic effect in the treatment of prostate cancer in a subject, where these substances vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

Finally, in light of the disclosure of Menshikowski et al. (*supra*), Rose et al. (*supra*), and Murkami et al. (*supra*), for example, it is apparent that the skilled artisan cannot predict whether the proliferation of prostate cancer cells can be inhibited using the claimed invention because, in part, it cannot be predicted whether the cells express the "PLA2" or "$sPLA_2$-IIA" that is targeted by any given inhibitor, it cannot be predicted whether the proliferation of the cancer cells will be sensitive to inhibition by any given inhibitor, and it cannot be predicted which substances are capable of inhibiting which "PLA2" or "$sPLA_2$-IIA" enzymes in the prostate cancer cells of any of the various different subjects that are encompassed by the claims.

Applicant is reminded therefore that the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v.*

Lederman, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). As discussed in greater detail below in the following rejection of claims, as lacking an enabling disclosure, there is in fact a very high level of unpredictability in the art, which is not been assuaged despite recent advancements in the knowledge and skill of the artisan.

For all of the above reasons, it is submitted that the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed, so as to satisfy the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

At best, the specification would only reasonably convey Applicant's possession of a method for inhibiting the proliferation of certain human prostate cancer cells, such as PC-3 and LNCaP, which express a human $sPLA_2$-IIA having an activity that is inhibited by the particularly described inhibitors "cFLSYR" and "c(2Nap)LS(2Nap)R"), which are analogues of the linear peptide consisting of SEQ ID NO: 5 (F-L-S-K-Y), as described by Tseng et al. (*J. Biol. Chem.* 1996 Sep 27; **271** (39): 23992-23998).

17. Claims 1-3 and 5-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a method for inhibiting the proliferation of certain human prostate cancer cells *in vitro*, such as PC-3 and LNCaP, which express a human $sPLA_2$-IIA having an activity that is inhibited by the particularly described inhibitors "cFLSYR" and "c(2Nap)LS(2Nap)R"), **and while being enabling for using** any process that is encompassed by the claims, which is taught by the prior art, **does not reasonably provide enablement for using** the claimed methods for inhibiting or reducing the proliferation of any prostate cancer cells and/or for treating prostate cancer in a subject, said methods comprising administering to the cells or to the subject any inhibitor of any "PLA2" or "$sPLA_2$-IIA" enzyme. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue”. These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained above, there is now a preponderance of factual evidence of record that, at best, the specification would only reasonably convey Applicant’s possession of a method for inhibiting the proliferation of certain human prostate cancer cells, such as PC-3 and LNCaP, which express a human $sPLA_2$-IIA having an activity that is inhibited by the particularly described inhibitors “cFLSYR” and “c(2Nap)LS(2Nap)R”), which are analogues of the linear peptide consisting of SEQ ID NO: 5 (F-L-S-K-Y), as described by Tseng et al. (*J. Biol. Chem.* 1996 Sep 27; **271** (39): 23992-23998).

This conclusion is largely based upon the disclosures in the specification, which show that the cyclic peptides designated “cFLSYR” and “c(2Nap)LS(2Nap)R” are capable of inhibiting the proliferation of two prostate cancer cell lines, namely LNCaP and PC-3, but incapable of inhibiting another (i.e., DU-145); see, e.g., Figure 4.

In contrast to the breadth of such a showing, the claims are far more broadly drawn to methods for inhibiting or reducing the proliferation of any prostate cancer cells and/or for treating prostate cancer in a subject, which comprise administering to the cells or to the subject any inhibitor of any "PLA2" or “$sPLA_2$-IIA” enzyme.

Applicant is therefore reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. “Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.” *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify a substance having the ability to inhibit an activity or biological function of a "PLA2" or “$sPLA_2$-IIA” enzyme, so as to be useful in practicing the claimed invention to achieve the claimed objective of inhibiting or reducing the proliferation of any prostate cancer cells and/or for treating prostate cancer in a subject; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

The specification describes the rationale that was used to develop the particularly described cyclic peptides designated “cFLSYR” and “c(2Nap)LS(2Nap)R”, which are shown to be capable of inhibiting the proliferation of LNCaP and PC-3 cells *in vitro*. At

paragraph [0143] of the published application, for example, the specification discloses the following:

> We have previously shown that human $sPLA_2$-IIA is dose-dependently inhibited by a pentapeptide sequence comprising residues 70-74 of the native sPLA.sub.2-IIA protein (^{70}FLSYK^{74}) (Tseng, A., et al., (1996) J. Biol. Chem. 271:23992-23998). Because of the inherent flexibility of the linear peptide sequence, inhibition was weak in in vitro activity assays. We have recently designed two novel cyclic peptides (Church, W. B. et al.), cFLSYR and a cyclic peptide where F and Y are substituted with 2-naphthylalanine (c(2NapA)LS(2NapA)R). Both have shown significant improvement in potency over linear peptides. The potent stimulatory effect of exogenous $sPLA_2$-IIA on prostate cancer cell number was completely blocked by the $sPLA_2$-IIA inhibitor, cFLSYR (FIG. 2B) at all concentrations tested.

However, the claims are not limited to these particularly described peptide analogues of the linear peptide first described by Tseng et al; and the specification discloses that the inhibitor can be virtually any substance that is capable of inhibiting a "PLA2" or "$sPLA_2$-IIA" enzyme, including, for example, peptides, peptidomimetics, proteins, antibodies, small molecules, and even antisense compounds, catalytic nucleic acids, or RNA inhibitors, which presumably inhibit the activity of a "PLA2" or "$sPLA_2$-IIA" enzyme indirectly by inhibiting the expression of the gene or the translation of the gene product; see, e.g., paragraphs [0050]-[0099] of the published application. Additionally, the specification discloses that the inhibitor is not limited to an inhibitor of the "$sPLA_2$-IIA" expressed by LNCaP and PC-3 prostate cancer cells, but may inhibit any "PLA_2" enzyme, including the type 1B, type IIA, type IID, type IIE, type IIF, type III, type IV, type V, and type X enzymes; see, e.g., paragraph [0013] of the published application.

Given the evident disparity in the breadths of the claims and the amount of guidance, direction and exemplification set forth in the specification, it is apparent that the specification would not have reasonably enabled the skilled artisan to make and then use at least a substantial number of such materially, structurally, and functionally varying inhibitors of such a large number of structurally and functionally varying enzymes, at least not without undue and/or unreasonable experimentation.

Then, even if the artisan were capable of making the various different inhibitors, it could still not be known or predicted which would be effective to inhibit or reduce the

proliferation of any prostate cell, including those of different mammals, and/or to treat prostate cancer in a subject.

Again, while the data presented in the specification demonstrate the inhibition of LNCaP and PC-3 cells that express "$sPLA_2$-IIA" upon contact with the cyclic peptide inhibitors designated "cFLSYR" and "c(2Nap)LS(2Nap)R", the specification also teaches the proliferation of DU-145 prostate cancer cells was not affected by either one of these inhibitors (paragraph [0148]; and Figure 4).

In fact, the disclosure fails to teach an inhibitor that inhibits an activity or function of a "PLA2" enzyme encoded by a gene that is expressed in the androgen independent prostate cancer cell line, DU-145; and the amount of guidance, direction, and exemplification that is set forth in this application would not reasonably enable the skilled artisan to make and then use an inhibitor of the activity of a "PLA2" or "$sPLA_2$-IIA" enzyme, which is effective to inhibit the proliferation of DU-145 prostate cancer cells.

As discussed in the written description rejection above, the differences described by Rose et al. (*supra*) between different the androgen independent prostate cancer cell lines PC-3 and LNCaP, together with the disclosure by Menshikowski et al. (*supra*) and the findings disclosed in the specification itself, underscore the high level of unpredictability in the art, and add to a bevy of data suggesting that the results of *in vitro* studies must be interpreted cautiously, since those results are not always extrapolated to predict the response of prostate cancer cells *in vivo*.

Kelland et al. (*supra*) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). Kelland et al. discusses, despite the limitations of xenograft models, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even in silico methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2).

Here, the only experiments disclosed are experiments that were conducted in vitro using three different prostate cancer cells lines: the androgen dependent LNCaP cell line, and the androgen independent cell lines, PC-3 and DU-145. No experiments

were performed *in vivo* using an appropriate animal model, such as the mouse xenograft.

Nonetheless, as noted, Kelland et al. (*supra*) addresses the limitations of such animal models.

In this regard, Kelland et al. teaches, though the successful use of such models in cytotoxic drug development is conclusive, today, there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of "molecularly-targeted", largely cytostatic drugs, such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse) immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1).

Gura (*Science.* 1997; **278**: 1041-1042) has also questioned the wisdom of conventional reliance upon the xenograft model to predict the outcomes of candidate therapies in humans. Gura teaches that although researchers had hoped that xenografts would prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, " '[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

Dennis (*Nature*. 2006 Aug 7; **442**: 739-741) echoes these concerns. Dennis reports, despite their present indispensableness, mouse models, such as xenografts, have only limited utility in predicting the clinical effectiveness of anticancer treatments; see entire document (e.g., page 739, column 2). Dennis explains there is a "laundry list" of problems associated with the use of mice to model human diseases, such as

cancer (page 739, column 1). Accordingly, Dennis reports, "[a]lthough virtually every successful cancer drug on the market will have undergone xenograft testing, many more that show positive results in mice have had little or no effect on humans, possibly because the human tumours are growing in a foreign environment" (page 740, column 1). Therefore, quoting Howard Fine, Dennis concludes: " 'Mice are valuable but they are, after all, still mice' ", suggesting the best study subject will always be the human (page 741, column 3).

Schuh (*Toxicologic Pathology*. 2004; **32** (Suppl. 1): 53-66) reviews the trials, tribulations and trends in tumor modeling in mice to disclose, for example, that "[c]ommon reliance on survival and tumor burden data in a single mouse model often skews expectations towards high remission and cure results; a finding seldom duplicated in clinical trials" (abstract). Furthermore, Schuh discloses, "[d]espite historical significance and ongoing utility, tumor models in mice used for preclinical therapeutic intervention often error towards false positive results and curing cancer in mice" (page 62, column 1). Given the noted limitations of xenograft models, Schuh suggests that testing in tumor-bearing animals may help to improve the predictive value of animal modeling; see entire document (e.g., the abstract).

Bibby (*Eur. J. Cancer.* 2004 Apr; **40** (6): 852-857) teaches that in the interest of finding more clinically relevant models, orthotopic models have been developed; see entire document (e.g., the abstract). In such "orthotopic" models, treatment is initiated after removal of the primary tumor and distant metastases are well established and macroscopic. These models have their advantages, but the procedures involved in using such models are far more difficult and time-consuming than conventional subcutaneous (e.g., xenograft) models; see, e.g., page 855, column 2.

Peterson et al. (*Eur. J. Cancer.* 2004; **40**: 837-844) teaches numerous agents have show exciting activity in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al. discloses, "have led to reasonable skeptism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that will have important clinical

utility" (abstract). Peterson et al. reviews the limitations of the xenograft models; see entire document (e.g., page 840, column 2).

Finally, Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Thus, taken collectively, there is a preponderance of factual evidence of record that the showing provided in the supporting disclosure would not have enabled the skilled artisan to practice the claimed invention, so as to achieve the claimed therapeutic objective in treating prostate cancer in subjects – not without undue and/or unreasonable experimentation, as required under the provisions of 35 U.S.C. § 112, first paragraph.

It is recognized that since the filing date sought by Applicant additional *in vivo* experiments have been performed using a xenograft mouse model of prostate cancer in which an immunodeficient nude mouse has been inoculated subcutaneously with PC-3 prostate cancer cells and treated with either one of the two cyclic peptides described in this application as being capable of inhibiting the proliferation of PC-3 cells in vitro (i.e., the cyclic peptides designated "cFLSYR" and "c(2Nap)LS(2Nap)R"). This study is described by Sved et al. (*Cancer Res.* 2004 Oct 1; **64**: 6934-6940); see entire document (e.g., the abstract).

First of all, it is important to remind Applicant that supporting documents of the sort cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. See M.P.E.P. § 2164.05(a).

Nevertheless, it is submitted that the results of the study described by Sved et al. (*supra*) fail to establish that the claimed invention can be used to inhibit or reduce the proliferation of any prostate cancer cell, either *in vitro* or *in vivo*, and/or to treat prostate cancer in a subject, such a human patient known to be afflicted by the disease.

In part, this is because, as explained in the preceding paragraphs, even encouraging preclinical studies in xenograft animal models have often failed to correctly predict the outcome of using the same therapeutic agents to treat the same disease in humans. As noted there are many reasons that the results of such studies poorly extrapolate to accurately infer or predict the effectiveness of candidate therapeutic agents and regimens in humans, but as an example, the results seen in the models are the effects of treating human tumors growing in the foreign environment of immunodeficient mice, which is a biological system that does not sufficiently mirror the variations and complexities of the clinical situation in the population of human patients.

In addition, it is noted that Sved et al. (*supra*) teaches that the cyclic peptide designated "cFLSYR" had no effect upon tumor burden in the mice when administered in a dose of 1 mg/kg; see, e.g., page 6939, column 1. Sved et al. teaches that only the cyclic peptide designated "c(2Nap)LS(2Nap)R" had any effect in the mice, when administered at this same dose, slowing the rate of growth of PC-3 tumors, as compared with the rate of growth observed in control mice that were not treated with the peptide (page 6939, column 1). The other peptide (i.e., "cFLSYR") was only effective when administered at a substantially larger dose of 10 mg/kg; see, e.g., page 6939, Figure 7.

Then, as described in the specification, Sved et al. (*supra*) also teaches the proliferation of LNCaP and PC-3 cells was inhibited the cyclic peptides designated "cFLSYR" and "c(2Nap)LS(2Nap)R", but the proliferation of DU-145 prostate cancer cells was not; see, e.g., page 9639, Figure 6.

Such variable sensitivity and other phenotypic differences between prostate cancer cell lines suggest that their use should not be relied upon in preclinical studies designed to ascertain whether the claimed invention might be used to achieve the claimed therapeutic effect in treating subjects afflicted by prostate cancer using the

claimed inhibitors. Again, Kelland (*supra*) notes, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even in silico methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Accordingly, despite the evident limitations of the xenograft models, Kelland et al. does not altogether discount the usefulness of such models. Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating prostate cancer, in general, using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not. Here, it is not known if the PC-3 xenograft model used, or the DU-145 xenograft model not used, might serve as the better model; so despite the encouraging results reported by Sved et al., any inferences based upon the results of a relatively limited analysis as to how effective the cyclic peptides described therein will be in treating prostate cancer in humans should be carefully deliberated.

In this regard, Menschikowski et al. (*supra*) discloses both PC-3 and DU-145 prostate cancer cells are highly aggressive, whereas LNCaP cells are not (page 284, column 1). The metastatic potentials of these different cells correlates with the expression of proangiogenic genes; and based on these properties, Menschikowski et al. (*supra*) discloses that the expression profiles of $sPLA_2$ isozymes suggest that $sPLA_2$-IIA plays only a secondary role, if any in tumorigenicity (page 284, paragraph bridging columns). As such, Menschikowski et al. (*supra*) suggests that additional studies are needed to elucidate the contributions of various $sPLA_2$ isozymes to proliferation, migration, invasion, cell-to-cell interaction, and other activities in prostate cancer cells (page 284, column 2).

In addition, Menschikowski et al. (*supra*) notes that although $sPLA_2$-IIA is not expressed in DU-145 cells, other $sPLA_2$ isozymes, such as $sPLA_2$-IIV might compensate for the loss in expression of the gene encoding $sPLA_2$-IIA (page 284, column 2). Not inconsistently, Murakami et al. (*supra*) suggests that type IIA and type V enzymes are functionally redundant and act in concert with cytosolic PLA2; see entire document (e.g., the abstract).

So will the blockade of the catalytic activity of human $sPLA_2$-IIA by the disclosed cyclic peptide designated "c(2Nap)LS(2Nap)R", for example, be sufficient to achieve therapeutic effect in treating prostate cancer, in general, in humans, or might the its lack of expression by DU-145 cells and/or the compensation of its loss of expression and/or activity by other PLA2 isoenzymes point to its non-essential nature in tumorigenesis and the progression of the disease?

It is not without additional studies that it will be known, and given the complexity and duration of such studies, for example, it is evident that the claimed invention is not reasonably enabled for use without undue and/or unreasonable experimentation

As a last point, with particular regard to claim 6-9, there is at least an implication in this application that the cyclization of a peptide capable of inhibiting an enzyme will make a more potent inhibitor[8]; however, there is evidence that the effects of cyclization or the induction of other conformation constraints upon the activity of a peptide inhibitor cannot be predicted, which suggests potentiation of inhibitory effects by an induction of conformation constraint cannot be expected.

In support of this position, Thwin et al. (*J. Med. Chem.* 2007; **50**: 5938-5950) describes their surprising finding that cyclization of a peptide that inhibits a $sPLA_2$ enzyme abolished the activity of the peptide, despite the fact that Church et al. (*J. Biol. Chem.* 2001 Aug 31; **276** (35): 33156-33164) demonstrated that cyclic peptides showed increased potency, as compared to their linear counterparts; see entire document (e.g., page 5943, column 2).

Claims 6-8 are directed to molecules or derivatives thereof that need not have any particular structure, but which function as an inhibitor of a "PLA_2" enzyme. The breadth of the claims is particularly evident in light of the definition of the term "derivative"; see, e.g., paragraph [0085] of the published application. According to this definition, the inhibitor might be a non-naturally occurring a-amino acid, which is an analogue of any of the amino acid residues at positions 70 to 74 of the amino acid sequence of human "$sPLA_2$-IIA" protein. While it is not reasonably expected that a non-

[8] See, e.g., paragraph [0143] of the published application, which cites Church et al.

naturally occurring amino acid will be found to inhibit a "PLA_2" enzyme, it is apparent that the amount of guidance, direction and exemplification provided in this application is not reasonably commensurate with the breadth of the claims, and would not enable the skilled artisan to make and then use such different inhibitors in practicing the claimed invention to achieve the claimed objective without undue and/or unreasonable experimentation.

As for claim 9, although the scope of the claim is considerably more limited, it still encompasses the use of analogues of the peptide first disclosed by Tseng et al. (*surpa*), which have not been shown to be effective to inhibit an activity of any a "PLA_2" enzyme, including a human "$sPLA_2$-IIA" enzyme. As evident from the disclosure of Thwin et al. (*supra*), the skilled artisan cannot always correctly predict the effect of derivatizing or making substitutions in the amino acid sequence of a peptide upon the activity of the peptide.

Consistent with this position, it is noted that Church et al. (*supra*) describes analogues of the peptide first disclosed by Tseng et al. (*surpa*), which lack the inhibitory activity of original peptide; see entire document (e.g., page 33158, Figure 1). In particular, Church et al. discloses that two peptides (i.e., "ALSYK" and "FLSYE" were inactive; and although active, two other peptides (i.e., "FLTYK" and "FWSYK") were considerably less inhibitory than the original peptide used as a positive control (i.e., "FLSYK") (page 33158, Figure 1).

The specification discloses, because of the inherent flexibility of the linear peptide sequence, inhibition by the original peptide described by Tseng et al. (*supra*) was weak, so Applicant began developing analogues of this peptide with the aim of developing a more potent inhibitor that might be useful in treating prostate cancer; see, e.g., paragraph [0143] of the published application.

Such disclosure implies that analogues of the original peptide described by Tseng et al. (*supra*), which are less inhibitory than even the original peptide, are not suitable for use in practicing the claimed invention.

Tseng et al. (*supra*) also describes two analogues of the originally described peptide inhibitor, including "KFLSY" and "LSYKF", but "LSYKF" and other analogues

were found to be wholly ineffective and “KFLSY” retained only a fraction of the inhibitory activity of "FLSYK"; see entire document (e.g., page 23997, Table III).

Church et al. (*supra*) describe a number of other analogues, but apart from the disclosed cyclic peptide and its cyclic analogues (i.e., “cFLSYK”, “cFLSYR” and “c(2Nap)LS(2Nap)R”) most were inactive or were only marginally more effective in the assays than the linear peptide (i.e., “FLSYK”); see, e.g., page 33159, Table I; and page 33161, column 2). Church et al. discloses that “cFLSYR” was 5-fold more effective in the assay, as compared to the originally described linear peptide, without disclosing or showing what improvement was achieved by the cyclization of the linear peptide to produce "cFLSYK" (page 33161, column 2). So, since as discussed above, Sved et al. discloses that only “c(2Nap)LS(2Nap)R” was effective *in vivo* at a dose of 1 mg/mg to slow the growth of PC-3 tumors in mice, whereas "cFLSYR" was not, it is reasonable to question whether "cFLSYK" could be used to achieve the claimed therapeutic effect in treating prostate cancer in a subject, particularly since Church et al. (*supra*) discloses that the peptides were toxic to cultured human cells at concentrations beginning at about 100 μM. As such, though the peptides may be effective inhibitors at certain doses, those doses may be too toxic to the subject to justify treatment; and perhaps only after additional studies are performed to access the effectiveness of each of the different peptides encompassed by the claims will it be known whether the claimed invention (or which embodiments thereof) can be used efficaciously to treat prostate cancer, in general, in subjects, particularly where those subjects are human patients.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

19. Claims 1-3 and 5-10 are rejected under 35 U.S.C. 102(a) as being anticipated by Sved et al. (*Cancer Res*. 2004 Oct 1; **64**: 6934-6940).

Sved et al. teaches the inhibition or reduction of the proliferation rate of LNCaP and PC-3 prostate cancer cells *in vitro* by contacting the cells with an inhibitor of the catalytic phospholipase A_2 activity of the $sPLA_2$-IIA enzyme expressed by those cells; see entire document (e.g., the abstract). In particular, Sved et al. teaches cyclic peptides designated "cFLSYR" and "c(2Nap)LS(2Nap)R" are effective inhibitors, which slowed the rate of growth of established PC-3 tumors in nude xenograft mice that received doses of either 1 or 10 mg/kg three times a week once the tumor had reached the size of 5 x 5 mm; see, e.g., page 6939, column 1.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Graff et al. (*Clin. Cancer Res.* 2001 Dec; **7**: 3857-3861) (of record; cited by Applicant) in view of Attiga et al. (Cancer Res. 2000 Aug 15; 60: 46-29-4637) (of record; cited by Applicant), Liu et al. (*J. Urol.* 2000 Sep; **164**: 820-825), or Kelavkar et al. (*Carcinogenesis*. 2001 Nov; **22** (11): 1765-1773).

Graff et al. teaches the expression of the gene encoding human $sPLA_2$-IIA is specifically increased with progression of human prostate cancer cells to androgen independence; see entire document (e.g., the abstract). Graff et al. teaches the expression of $sPLA_2$-IIA is inversely related to patient survival; see, e.g., the abstract. Accordingly, Graff et al. teaches their report "provides compelling evidence that enhanced sPLA2-IIa expression may be involved in the malignant progression of human prostate cancer and suggests that specific inhibitors of the group IIa sPLA2 may be useful for prostate cancer chemotherapy" (page 3860, column 2).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have inhibited the growth or proliferation of prostate cancer cells by contacting the cells with an agent that inhibits the expression and/or activity of human $sPLA_2$-IIA in prostate cancer cells. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so in order to treat prostate cancer.

One ordinarily skilled in the art at the time the invention was made would have had a reasonable expectation of successfully doing so in light of the disclosure of Attiga et al., Liu et al., or Kelavkar et al.

Attiga et al. teaches eicosanoids modulate the interaction of tumor cells with various host components in cancer metastasis, and their synthesis involves the release of arachindonic acid from cellular phospholipids by phospolipase A_2, followed by metabolism by cyclooxygenases and lipoxygenases; see entire document (e.g., the abstract). Attiga et al. teaches the invasion of prostate cancer cells (i.e., PC-3 and DU-145 cells) is inhibited by a PLA2 inhibitor, a general cyclooxygenase inhibitor, and a selected COX-2 inhibitor; see, e.g., the abstract. Attiga et al. teaches treatment of the cells with these inhibitors reduced their secretion of matrix metalloproteinases; see, e.g., the abstract.

Liu et al. teaches the growth of PC-3 xenograft tumors in nude mice was inhibited by a COX-2 inhibitor; see entire document (e.g., the abstract). Liu et al. teaches COX-2 inhibition is even more effective *in vivo* than might be predicted because treatment of prostate cancer cells with the inhibitor induces the cells to undergo apoptosis and

causes down-regulation of the gene encoding VEGF, so as to have anti-angiogenic effects; see, e.g., page 820, column 2.

Kelavkar et al. teaches the gene encoding 15-lipoxygenase-1 is overexpressed in PC-3 prostate cancer cells, and that aberrant expression of enzymes that convert unsaturated fatty acid arachidonic acid and linoleic acid to bioactive lipid metabolites appears to significantly contribute to the development of prostate cancer; see entire document (e.g., the abstract; and page 1765, column 2). Kelavkar et al. teaches that overexpression of 15-lipoxygenase-1 by PC-3 cells leads to the up-regulation of the gene encoding VEGF; see, e.g., page 1771, column 2. Kelavkar et al. teaches that the proliferation of PC-3 cells is inhibited by treating the cells with an inhibitor of 15-lipoxygenase-1; see, e.g., the abstract.

Thus, in view of the disclosures of Attiga et al., Liu et al., or Kelavkar et al., one ordinarily skilled in the art at the time the invention was made would have had a reasonable expectation of successfully practicing the claimed invention because PLA_2 (e.g., $sPLA_2$-IIA) acts upstream of the cyclooxygenases and lipoxygenases, which in turn act to convert unsaturated fatty acid arachidonic acid and linoleic acid to bioactive lipid metabolites that contribute to the development of prostate cancer. Because inhibition of the cyclooxygenases and lipoxygenases has proven effective to inhibit the proliferation of prostate cancer cells, as well as the spread of the cancer by anti-angiogenic mechanisms, the artisan would reasonably expect that the inhibition of $sPLA_2$-IIA in prostate cancer cells will result in the inhibition of their proliferation by inhibiting the activities of the cyclooxygenases and lipoxygenases acting downstream of PLA_2 in the pathway leading to the production of the eicosanoids, such as prostaglandins and leukotrienes, as well as in the regulation of the gene encoding VEGF.

22. Claims 5-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Graff et al. (*Clin. Cancer Res.* 2001 Dec; **7**: 3857-3861) (of record; cited by Applicant) in view of Attiga et al. (Cancer Res. 2000 Aug 15; 60: 46-29-4637) (of record; cited by Applicant), Liu et al. (*J. Urol.* 2000 Sep; **164**: 820-825), or Kelavkar et al.

(*Carcinogenesis*. 2001 Nov; **22** (11): 1765-1773), as applied to claims 1-3 above, and further in view of Church et al. (*J. Biol. Chem.* 2001 Aug 31; **276** (35): 33156-33164).

Graff et al. teaches that which is set forth in the above rejection of claims 1-3 under 35 U.S.C. § 103(a), but does not expressly teach or suggest that the $sPLA_2$-IIA inhibitor is a cyclic peptide or analogue derived from the linear peptide first described by Tseng et al. (*supra*), which is a peptide consisting of the amino acid residues at positions 70-74 of a purified human $sPLA_2$-IIA protein.

Church et al. describes the identification of a peptide consisting of the amino acid residues at positions 70-74 of a purified human $sPLA_2$-IIA protein, which is capable of inhibiting the catalytic activity of $sPLA_2$-IIA; see entire document (e.g., the abstract). Church et al. teaches this peptide, first described by Tseng et al. (*supra*), consists of the amino acid sequence: F-L-S-Y-K; see, e.g., the abstract. Church et al. teaches cyclization of the peptide or of an analogue (i.e., F-L-S-Y-R) increased the inhibitory potency of the peptide, as compared to the original peptide; see, e.g., page 33161, column 2. However, Church et al. further discloses that a cyclic analogue of the peptide in which the phenylalanine and tyrosine residues are replaced by 2-naphthylalanine is even more potent; see, e.g., page 33161, column 2. Church et al. designates this cyclic analogue: "c(2NapA)LS(2NapA)R"; see, e.g., page 33162, Table II.

Accordingly, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have inhibited the growth or proliferation of prostate cancer cells by contacting the cells with the cyclic peptides described by Church et al., which were demonstrated to be highly potent inhibitors of $sPLA_2$-IIA, such as the peptide designated by Church et al. as "c(2NapA)LS(2NapA)R". One ordinarily skilled in the art at the time the invention was made would have been motivated to do so in order to treat prostate cancer.

Again, one ordinarily skilled in the art at the time the invention was made would have had a reasonable expectation of successfully doing so in light of the disclosure of Attiga et al., Liu et al., or Kelavkar et al.

Conclusion

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/

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slr
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